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SEP 3 1947

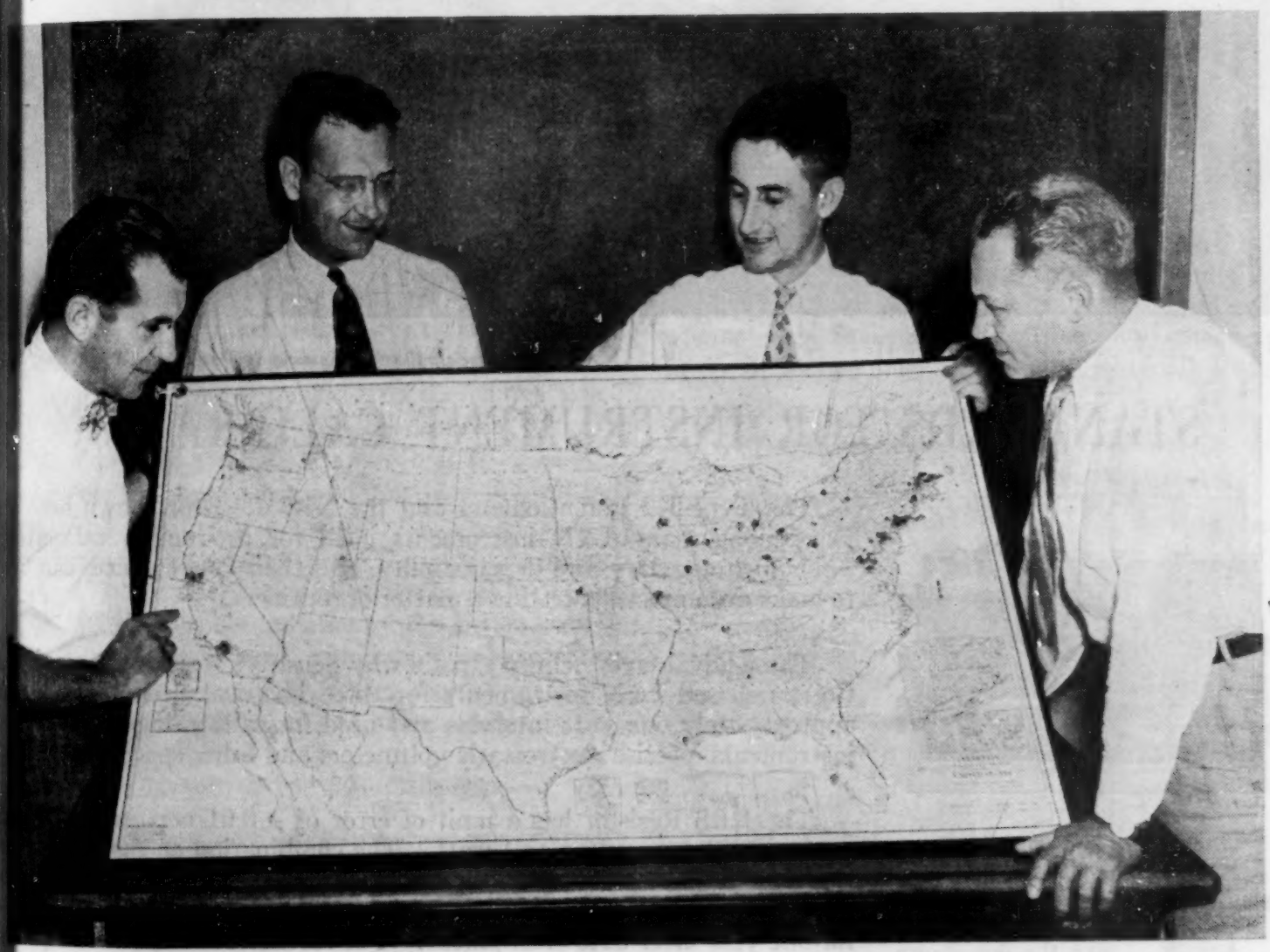
Vol. 106
No. 2748

Pages 175-194

August 29, 1947

Science

THE SCIENTISTS NEWSWEEKLY



Locations of medical and scientific institutions using radioisotopes are indicated on map of United States being examined by P. C. Aebersold, chief, Isotopes Branch, U. S. Atomic Energy Commission; N. W. Woodruff, of the Commission; J. A. Cox, Clinton Laboratories; and E. J. Murphy, assistant research director, Clinton Laboratories (*left to right*).

Published by the
AMERICAN
ASSOCIATION
FOR THE
ADVANCEMENT
OF SCIENCE

The Isotope Distribution Program

U. S. Atomic Energy Commission

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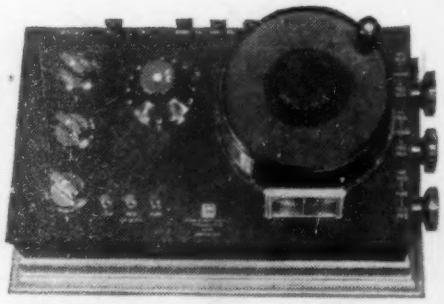

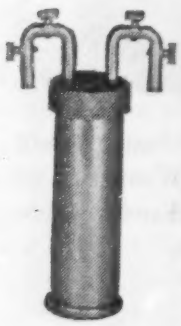

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The Isotope Distribution Program

Isotopes Branch, U. S. Atomic Energy Commission

ON JUNE 14, 1946, HEADQUARTERS OF the Manhattan Project first announced in *Science* a program for production and distribution of pile-produced radioactive isotopes for use in the Nation's scientific, technical, and medical investigations. On August 2 the first shipments of radioisotopes were made. On January 1, 1947, this program, with a fine record of five months of successful operation, was taken over, along with other operations of the Manhattan District, Corps of Engineers, by the U. S. Atomic Energy Commission.

With the passing of the one-year mark of isotope distribution it is appropriate that this journal, the official publication of the American Association for the Advancement of Science, should be the medium through which a report on the program is made. Numerous published technical articles have appeared on work achieved with distributed isotopes. A number of announcements on additional isotope distribution service have been published in the scientific journals, and popular releases on the uses of isotopes have appeared in the press and magazines. It has, however, been called to our attention by scientific and medical advisory groups that an occasional summary report of the over-all developments and accomplishments of the program should be published for the information of the Nation's scientific and technical personnel.

The Commission is indeed aware that it exercises a virtual monopoly in the distribution of many isotopes and that this distribution is now essential to a wide range of investigations and applications. The scientific importance of isotope distribution is evidenced by the report which follows. It is the intention of the Commission to press the program forward, within the provisions of the Atomic Energy Act of 1946, with a view to increasing benefit to scientific advance and human welfare.

Distribution of Radioisotopes

During the first year of distribution, pile-produced radioisotopes were shipped to over 160 institutions and organizations, representing more than 240 departments and 500 groups located in 31 states and in the Territory of Hawaii. Users in four states (California, Massachusetts, New York, and Pennsylvania) account for nearly half the shipments (Table 1). In the first 12 months of the program over 1,100 shipments had been made.

If the recipients are divided into four main categories, the number of institutions in each is approximately as follows: medical institutions and hospitals (including medical schools), for use in therapy, diagnosis, and research, 60; educational institutions (mainly universities), for use in research, 50; industrial and profit organizations, for use in both fundamental and applied research, 35; public and private nonprofit research institutions (other than educational), for use in fundamental and applied research, 20.

TABLE 1

Distribution of Radiomaterials by Location

(First 12 Months—to July 31, 1947)

State	No. of institutions	No. of shipments
New York	26	153
California	16	104
Pennsylvania	15	66
Massachusetts	13	169
27 other states and Hawaii	90	609
Total	160	1,101

About 60 different radioisotopes were shipped—a major portion of available kinds. In Table 2 are shown data on the total number of shipments in each of several major categories of available isotopes. Fission products have been grouped as one entry, as have most of those radiomaterials furnished without chemical processing (*i.e.* in "irradiated units" of the target material). P^{32} and

TABLE 2

Distribution of Radiomaterials by Isotopes

(First 12 Months—to July 31, 1947)

Radiomaterial	No. of shipments
C^{14} (separated)	99
P^{32} (separated)	261
P^{32} {unseparated in sulfur}	1
P^{32} (in phosphate)	52
I^{131} {unseparated separated}	313
I^{131} (in tellurium)	9
S^{35} (separated)	12
S^{35} {unseparated in chloride}	22
10 isotopes of fission products (separated)	17
40 isotopes in irradiated units (unseparated from target materials)	307
Service irradiations	8
Total shipments	1,101

I^{131}, used chiefly in medical diagnosis and therapy, constitute the largest number of shipments of chemically separated radioisotopes. These two also account for the largest total activity shipped in the form of separated isotopes (over 10,000 millicuries each). It is particularly noteworthy that the first year's distribution included over 90 shipments of C^{14}, with a total activity of about

130 millicuries. This quantity of the extremely important isotope, C^{14}, is millions of times greater than that heretofore available for investigations.

Uses of Distributed Radioisotopes

Hundreds of different uses are being made of distributed radioisotopes. The number of individual phases of investigation being undertaken is difficult to estimate but is certainly over 1,000.

The types of investigational problems in progress with the distributed radioisotopes are as varied as the interests and imaginations of the investigators. Most of the studies could not be approached satisfactorily, if at all, in any other way. It is not appropriate here to attempt to list or discuss the many types of uses. A general discussion and a few specific cases will, however, be enlightening.

From a functional standpoint, uses of radioisotopes may be classed as follows: tracer investigations (including medical diagnosis), medical therapy, sources of radiation for physical applications (radiography, etc.), and studies of nuclear properties and phenomena. The first two types of uses far outweigh the others in number and importance. As noted above, a fairly large number of medical institutions are using radioisotopes for medical therapy, diagnosis, and research. Tracer investigations, of course, promise a vast extension of knowledge in many fields, and their ultimate value to human welfare may far exceed that of the other applications of isotopes.

From the standpoint of fields of investigation, the uses of radioisotopes can be classified roughly into 9 groups, although most of the work has been done in the fields of medical therapy and physiology (animal and human). Agriculture, plant physiology, industrial research, chemistry, and physics account for most of the remainder, with lesser amounts of work being done in microbiology (bacteriology) and metallurgy. Many specialized phases related to the above fields are represented, such as animal husbandry, biochemistry, dentistry, entomology, industrial hygiene, petroleum engineering, pharmacology, radiology, soil science, surgery, toxicology, veterinary medicine, and zoology.

An appreciation for the scope of radioisotopes as tracers in biological and medical research can be gained from the following list of some of the biological materials that are being labeled and traced: alcohols, amino acids, antigens, bacteria, bile acids, blood cells, carbohydrates, carcinogens, enzymes, fats, fatty acids, hormones, insulin, nucleic acids, penicillin, pharmaceutical agents, proteins, starches, sulfa drugs, tissue fluids and salts, viruses, and vitamins. The synthesis, utilization, and excretion of such labeled materials are studied in the organs and tissues of a wide variety or organisms (plants, animals, and man).

Therapy of hyperthyroidism and certain thyroid cancers with I^{131} has been employed rather extensively as has that with P^{32} in the treatment of polycythemia vera and other blood dyscrasias. One laboratory has extensively tested the therapeutic value of colloidal radiogold (Au^{198}) in cases of lymphoid malignancy. Several others are testing the efficacy of certain radioisotopes in beta-ray applicators and in colloids for treatment of local lesions.

I^{131} has been used in studies of the fundamental metabolism of the thyroid gland. A considerable number of workers are attempting to elucidate the mechanism of both carbohydrate and protein metabolism by use of compounds labeled with C^{14}. A variety of problems, including those of bone and tooth formation, have been attacked by using radiocalcium and radiophosphorus. Radioiron is being used in studies of blood function, and radiosodium has been employed in the study of water balance and blood flow.

Of all the studies in plant physiology the most dramatic is probably the effort to learn the mechanism of photosynthesis by use of C^{14}, but others have initiated studies to increase our knowledge of the absorption by plants and animals of phosphorus, calcium, iron, potassium, and some trace elements by using the appropriate radioisotope in each case.

Many other studies related to agriculture are in progress, including storage in soil and uptake by crop plants of fertilizers and other soil additives; action of insecticides, fungicides, and weed killers on insects, plants, and animals; effects of industrial vapors and wastes on plants and animals; deficiency diseases and utilization of foods and essential minerals in crops and livestock.

In chemistry the principal emphasis has been on the use of labeled molecules in the study of reaction and exchange mechanisms. A similar effort is being made in certain industrial research work, notably in the field of catalysis in hydrocarbon reactions.

Physicists have used a goodly number of radioisotopes in their effort to arrive at more exact measurements of disintegration patterns.

A unique approach to the industrial hygiene problem of removal of air-borne toxic and infectious materials has been made possible by studying the capacity of filters and exhaust systems to remove finely atomized radioactive materials of short half-life.

Increasing applications are being made in industrial problems. These include investigations on friction, lubrication, diffusion, aging and oxidation of metals, kinetics of reactions in solid alloys, control of impurities in metal melts, petroleum cracking, oil field logging, and chemical process efficiencies.

Improvements in Availability of Radioisotopes

The initial announcement on the availability of pile-produced radioisotopes listed 80 procurable radioisotopes. It was emphasized in the announcement that none of the radioisotopes was yet in routine production. For a few isotopes only, production processes were under technical

development. For most isotopes, processes were largely in the research or then untried stages.

During the elapsed year, Clinton Laboratories, Oak Ridge, Tennessee, the supplier, has achieved much progress in routine production of many items and has made significant improvement in the form and availability of those materials not yet in routine production. Production of the majority of items is now adequate to meet the legitimate demands of all users who can handle the materials effectively and safely. In addition, it has been possible to add 16 procurable radioisotopes to the list originally released to *Science*.

Investigators may also now secure service irradiations of their own materials when necessary. Special chemicals and other materials (suitable for exposure in the Clinton pile) may be subjected to pile irradiation. This enables qualified personnel to study the effect of pile irradiation on crystals, organic chemicals, seeds, intact metal parts, and numerous other materials of special interest. The Argonne National Laboratory, Chicago, Illinois, has also recently undertaken to perform certain service irradiations for qualified investigators by means of the Argonne heavy-water pile.

Improved and large-scale methods of producing C^{14} have permitted a significant reduction in the cost of this important item from $367 to $50 per millicurie.

Chemically separated S^{35} of high specific activity has been made available in the form of labeled H_2SO_4 and Na_2S. Increased yield in extraction of S^{35} (from irradiated chlorine compound) has also made possible lower prices on these items.

Improvements in the processes of extraction of P^{32} and I^{131} (from irradiated sulfur and tellurium, respectively) now enable the supplier to meet more rigid specifications on the chemically separated forms of these isotopes. This is important, since the materials are being extensively used in medical investigations on human beings, both in diagnosis and therapy.

Small quantities of chemically separated Ca^{45} of high specific activity have just become available. This isotope is produced by transmutation reaction in scandium. When extraction procedures have been developed further, the material should become routinely available.

Some of the important tracer radioisotopes, such as radioiron, radiocalcium, and radiochlorine, originally available only with low specific activity, are now being made available with much higher specific activity.

C^{14}-labeled compounds (other than $BaCO_3$) are being prepared by several Commission laboratories for their research programs. However, excess quantities of certain compounds can be synthesized for use by laboratories outside the Commission. C^{14}-labeled methanol (C^*H_3OH) is currently available, and C^{14}-labeled barium carbide and sodium formate should be available soon. Additional C^{14}-labeled compounds, useful largely as intermediates, are expected to become available also.

Availability, Distribution, and Use of Stable Isotopes

During the 7 months that the distribution program has been under the control of the Atomic Energy Commission, enriched forms of three stable isotopes have been made available. Heavy hydrogen is available as deuterium gas and heavy water, in which the ratio of the hydrogen isotopes is 99.8 deuterium to 0.2 protium. Boron is available in calcium fluoride-boron fluoride complex containing B^{10} concentrated to 96 per cent of the boron content (or about 5-fold enrichment of B^{10}). O^{18}, with a concentration about 7 times that in nature, is available in water in which the deuterium is not enriched.

Since the May 1, 1947, announcement of deuterium distribution, over 75 research groups in all parts of this country have been allocated an equivalent of about 28,000 grams of deuterium oxide. Lower price and greater availability of the material are permitting extensive and new uses of deuterium. Studies that were previously unfeasible are now being made in humans.

The deuterium or deuterium oxide is being used to supply bombarding deuterons for cyclotrons and other nuclear accelerating devices at 18 research institutions. Other applications in physics include: absorption spectra of deuterium-substituted inorganic and organic compounds; piezoelectric property of deuterium-containing crystals; photodisintegration of deuterons; filler for high-pressure cloud chambers; calibration of mass spectrometers; and molecular moment studies.

In chemistry deuterium is being employed to synthesize substituted compounds such as deuterium-labeled benzene, aliphatic hydrocarbons, and halogenated fatty acids, which are studied for their physical and chemical properties. The mechanisms of certain chemical reactions are very easily investigated with heavy hydrogen.

Deuterium is also serving as a tool in many biological and medical investigations. Biosynthesized tyrosine being labeled with deuterium will be used to study the metabolic aspect of this material. Studies of total body water and extracellular fluids in various physiological conditions of the human body are being made with heavy water, as are metabolism studies involving amino acids, bile acids, fatty acids, tryptophane, glycogen, nicotinic acid, etc.

Eleven leading institutions conducting nuclear research have received allocations of the complex containing B^{10}. Although B^{10} is being used chiefly in the preparation of ionization chambers and counters for neutron detection, some investigators indicate that studies of nuclear reactions of B^{10} will be made.

Since distribution of O^{18} has only recently been announced, no report is made on this item. Because of the relatively low enrichment of the material, it will in most cases be enriched further before use by several groups who have set up equipment suitable for the purpose.

Health Protection

Radioisotopes will perhaps find their greatest application when employed in small quantities as tracer substances rather than in large quantities as therapeutic or industrial agents. However, because of the radioactivity involved, any application requires certain fundamental knowledge for effective and safe use of radioisotopes.

Information on health protection is one of the most frequent requests received in connection with the program. Several circulars on health protection are available, and further informational circulars on medical and health protection measures are being prepared for distribution to radioisotope applicants and users.

For practical purposes, health protection may be considered as presenting two individual but related problems. The first, which is largely medical, consists of determining experimentally the biological effects of radiations and radioactive materials and of checking for possible radiation effects in the body. This is essential for the safeguarding of personnel using radioactive materials. Experiments are being conducted, and the results being made known, on the toxicity and radiation effects which may be produced by a wide variety of radioisotopes. Although we now have certain indices which are of value, improved methods of detecting possible radiation effects are continually being sought.

The second problem is largely physical and bears a causal relationship to the first. It is known as "health-physics." By this term we connote all those precautionary measures of routine monitoring, adequate shielding, handling techniques, decontamination, etc. which serve to avert any excess exposure to radioactivity. Research and development is under way to improve such measures.

Advisory Field Service

In view of the general need for health protection assistance in the use of radioisotopes, the Atomic Energy Commission has established, in conjunction with the distribution program, an Advisory Field Service. When a specific need for this service is indicated, it is provided to isotope users without charge. Its prime objective is to render assistance, information, and consultation on all matters of health protection. When feasible, it will attempt to advise and make available information on new techniques of measurement and application.

The service, which functions through the Isotopes Branch, now has a physician and health-physicist available for consultation. Although the service is at present limited to those in most need of it, it may be expanded as deemed necessary.

Instrumentation

During the war, manufacturers of radiation-measuring instruments diverted their entire production to wartime needs. The Manhattan Project was the largest single customer. The Atomic Energy Commission still requires a large number of the produced instruments to continue its work most effectively. Instrument-manufacturing companies, which now include many new firms, are, however, becoming increasingly able to meet demands from the open market.

Most types of radiation instruments developed on the Manhattan Project have been declassified and are already, or soon will be, commercially available. The Commission is continuing with vigor the policy of licensing for commercial production and sale those radiation instruments developed within its facilities. Commercial firms have also undertaken considerable development in instrumentation. Increasing availability of many types of improved radiation-detection instruments is therefore expected. The Isotopes Branch, upon request, will furnish lists of manufacturers and offer assistance concerning types of radiation instruments which will facilitate an investigator's work.

Declassification of Pertinent Information

Of the many Commission research reports written in connection with the development of atomic energy, three types—those on medical, health-physics, and instrumentation matters—are of special interest to the users of radioactive isotopes. Authors of reports falling in these categories are being encouraged to submit them for declassification, and to date more than 125 such documents have been declassified. A large number of these reports are available to the public through publication in widely circulated scientific journals. Copies may also be obtained through the Office of Technical Services of the U. S. Department of Commerce.

Procurement

The situation is good for procurement of most isotopes offered by the Commission. The stocks of stable isotopes are adequate for most uses. (C^{13} and N^{15} are not procurable from Commission facilities, but are obtainable in good supply from commercial firms.) Many of the chemically separated radioisotopes are produced regularly to keep supplies currently available. Other radioisotopes are separated in batches as demands arise. Radiomaterials furnished without processing are usually produced only after receipt of a purchase order by the supplier. A week to several months is then required, depending on the isotope desired. Details concerning availability and procurement of isotopes and related information and services may be obtained by writing the Isotopes Branch, Atomic Energy Commission, P. O. Box E, Oak Ridge, Tennessee.

The Isotopes Branch serves as an information and allocation agency, while production and distribution are accomplished by organizations under contract with the Commission. Submission of purchase orders and arrangements with the supplier concerning specifications and

shipments of materials are made only after allocation. Allocations can be obtained in one to three weeks after submission of properly completed request forms, the time depending on action that may be necessary by advisory allocation groups.

Although it is not possible in this limited space to give due credit to all individuals who have contributed to the success of this program, it is possible to designate certain organizations and groups which have made enormous contributions.

The Clinton Laboratories pile has been chiefly responsible for the production of radioisotopes, although piles of other areas have been used to some extent.

The preparation of chemically separated radioisotopes has been accomplished through the cooperative activities of the Chemical, Technical, and Production Divisions at Clinton Laboratories, operated for the Government by the Monsanto Chemical Company.

The Chemical Division at Clinton Laboratories and various groups at the Argonne National Laboratory and Radiation Laboratory of the University of California have made numerous contributions to basic radiochemical and physical techniques which aided the development of presently employed processes.

Matters pertaining to scheduling, shipping, and billing have been efficiently handled by the management and other groups at Clinton Laboratories. The Health-Physics Department there has given expert supervision to the safety and health protection phases of packaging and shipment.

Production of deuterium gas from deuterium oxide as well as the shipping and billing for the produced gas and deuterium oxide are being managed by Stuart Oxygen Company, San Francisco, California. The deuterium oxide was produced by facilities contracted for by the Manhattan Project.

Allocations by the Atomic Energy Commission have been made by the Isotopes Branch with the assistance of advisory committees composed of personnel outside the Commission staffs. Each request has been reviewed and rated on its individual merits by subcommittees on allocation and on human applications. These advisers are as listed in the original announcement in *Science*. Their continuing service, which is voluntary, is indeed keenly appreciated.

The success attained in the isotope distribution program has been the result of cooperation of a number of organizations and hundreds of interested persons. The Commission appreciates the fact that it can rely on the continued cooperation and efforts of these individuals, as well as on further participation by others. Increasing success of the program is therefore guaranteed.

Suggested Principles of "Social Physics"

John Q. Stewart

Princeton University Observatory, Princeton, New Jersey

A NEW DEMOGRAPHIC INDEX, CALLED "potential of population," was found in 1940 (*1*). Studies have been resumed, and it is now established that, when averages are considered, principles resembling some of those of physics apply not only in demography but in related aspects of economics.

When celestial mechanics was being developed, in the 16th and 17th Centuries, the order of advance was: (1) the collection of quantitative observations (Tycho Brahe); (2) their condensation into empirical mathematical regularities (Kepler); and (3) theoretical interpretation of the latter (Newton). If there is to be a social physics, its beginnings must follow the same standard pattern. During recent years, social statisticians have published amazing amounts of numerical observations. That stage is well advanced. Several pioneers (especially G. K. Zipf and A. J. Lotka) have described significant empirical regularities. A great deal more attention must, however, be given to the third stage by numerous investigators before it is fully achieved.

Mathematical rules in demography are described in a current report (*2*) which contains numerous references to previous work. Intensive further studies have been carried on with the cooperation of the School of Economics and Politics of the Institute for Advanced Study. Only a partial and condensed description of these can be given below.

An important empirical relation is found between the population and the average area of cities in the U. S. Census of 1940, namely,

$$A = \frac{P^{\frac{4}{5}}}{350},$$

the area, A, being in square miles. This is the land area of the "political" city, within the official city limits. The rule holds statistically for cities above the rural limit of 2,500, including the largest ones. Examination of less inclusive data published by the Bureau of the Census for 1890 shows that the same formula applied, except that the numerical constant was 400 instead of 350. That is to

say, a city of any assigned population averaged no more than 6 or 7 per cent larger in linear dimensions in 1940 than in 1890, notwithstanding the development of rapid transit.

The existence of this conspicuous regularity demands the existence of additional ones in the average distribution of people within each city. For each of 60 leading cities in 1940 the internal distribution of population by "census tracts" is available. There is strong evidence for the following standard internal pattern, as a first approximation: The normal city, regardless of size, has roughly the same density of population at its edges, averaging there about 3 people per acre or 2,000 per square mile. From edge to center, the density tends to increase exponentially with the distance, reaching a peak density in some inner census tract which usually is adjacent to others having densities nearly as great. The peak density tends to increase with the size of the city, reaching in 1940 more than 400 per acre in Manhattan (Avenues B to D, 3rd to 9th Streets).

The "demographic gravitation" implied by various applications of the concept of potential of population serves to account in part for these facts. But a statistical countertendency is required to explain why all the people in a city do not pile up in the most dense census tract. An adequate mathematical description of this appears to be found in the concept of the "human gas." Each individual seeks some elbowroom or living space. The idea of a two-dimensional gas is already familiar in physics (monomolecular layers). In the demographic analogue we write: $pa = NT$, where a is the area occupied by N individuals (molecules), p is the "demographic pressure," and T is the "demographic temperature." In the physical case, p is the force per unit length of boundary.

Since the well-to-do normally live in larger quarters than the poor, the use of per-capita rent suggests itself as a measure of demographic temperature. This, in turn, following obvious physical analogues, leads to the interpretation of the "demographic energy," NT, as value or wealth. The quantity T can be measured by the value per capita of the land plus improvements, while p is its value per unit area. In general, the "demographic force" is interpreted as the rate of change of a value with distance.

The high land-value per acre reached in cities is a consequence of demographic gravitation. People gather in urban concentrations because both the means of livelihood and the material services which enhance living can be more varied and abundant in such situations. The suggested combination of gravitation and the gas laws is already a familiar pattern in astrophysics, in the elementary theory of stellar constitution.

Confirming the above ideas, a relation at once follows to the previously observed average dependence of the density of rural population on the potential of population (*1*). Not only in 1930, but also in 1940, 1900, and 1840, the rural density in the United States tended to vary as the square of the potential. Cities are "anchored" in place by special considerations (often topographic), but the rural population can distribute itself with relatively little distortion by sharply local influences. In order for the density of a perfect gas to vary as the square of the gravitational potential, the temperature, as can easily be shown, must vary as the potential. Full data concerning rents are available in the Population and Housing series of the U.S. Census of 1940. It is a fact that in the 28 states east of Colorado and north of the Deep South—where the rural density rule held especially well—the rural nonfarm rent was, on the average, proportional to the first power of the potential of population.

This result leads to a dollar quotation (or conversion factor) for the demographic unit of value—the value of the propinquity of two people placed one mile apart, as evidenced in the value of land. It was of the order of half a cent in 1940, in terms of capitalized rural rent.

A rough survey of rural land values at different times and different places in the United States suggests that the dollar quotation of the unit of propinquity has been much less unstable than the cost of living. Indeed, the speculative suggestion may be made that the secular increase in the latter has not been produced by inflation in the value of the demographic unit, but by the continued growth of population. That has increased the number of units of propinquity involved in normal subsistence.

Just as the telephone subscriber on a large exchange must pay more because he can make more different calls than the subscriber on a small one, so the individual in the United States of the present is involved in many more possible relations with his fellows than when our population was smaller. The number of relations of N_1 people who are at a distance d from N_2 people is proportional to N_1N_2/d; this is the demographic energy. The introduction in this formula of the factor of inverse distance agrees with common sense, but its final justification is found in a large variety of statistical evidence in the social field.

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2. Stewart, John Q. *Geogr. Rev.*, July, 1947.

Association Affairs

eeting of Southwestern ivision

The first postwar meeting of the Southstern Division, AAAS, was held in olorado Springs, May 1–3, in conjunon with the Colorado-Wyoming Acadny of Science. Societies meeting in sociation with the Division were the earing House for Southwestern Muums, the Colorado-Wyoming Chapter of e American Association of Physics achers, the Colorado-Wyoming Social ience Association, the Rocky Mountain anch of the American Psychological ssociation, the New Mexico Academy of ience, and the Colorado College Chapr of the American Association of Uniersity Professors. Colorado College rved as host institution, all the meetings ing held on its campus.

A total of 158 papers covering a wide eld of effort were presented in the 11 secons as follows: Bacteriology, 9; Plant ience, 30; Zoology, 16; Anthropologyrchaeology, 6; Education, 4; Psycholgy, 15; Social Science, 4; Chemistry, 25; eology-Geography, 33; Physics, 13; and e American Association of Physics eachers, 3. A comparison of the total of 50 officially registered scientists with the 58 papers presented shows that many ersons attended only to listen and learn. his feature of educating the nonspecialist o what the researcher is doing is often verlooked by those presenting papers. ll too frequently the speaker, no doubt ecause of time limitations, starts off in he middle of the subject, assuming equal amiliarity with his specialty on the part f his listeners. The result is that no one is ducated except specialists in his own eld.

It may well be assumed that many who present papers at scientific meetings would not attend if they were not on the program, since their papers, if real contributions to science, would eventually be published and made available to scientists generally. One frequently hears the comment that because scientific sessions are too technical to be understood it is unnecessary to attend them, and that the chief value in attendance lies in the people one meets and talks to in the corridors. If this is true, more attention should be given to demanding that papers submitted for presentation be truly informative to the nonspecialist, to keeping the number of papers down, and to giving each speaker sufficient time not only to present new facts but also to lay a foundation for his subject. At present it is difficult to find cities willing and able to serve as hosts to large conventions. Would it not be wise to reduce the number of papers, require that they be truly informative, and thus bring science to the community in which the meeting is being held?

A high light of the meeting was the annual John Wesley Powell Lecture, delivered by John H. Manley, executive secretary of President Truman's General Advisory Committee to the U. S. Atomic Energy Commission, and a former head of the research division, Los Alamos Scientific Laboratory. His address was entitled "One Atom and Many."

The address of the retiring president, H. P. Mera, given following the annual dinner, was entitled "Archaeological Research in the Southwest." This stressed the importance of using the findings of archaeological research to guide future actions of man in order to avoid the catastrophes causing the disappearance of previous civilizations. He warned against a mere multiplication of findings of things already known by excavations of sites similar to those studied by previous workers.

Officers elected were: F. H. Douglas, Denver Art Museum, president; Ernst Antevs, Globe, Arizona, vice-president; H. P. Mera, Santa Fe, and Edna L. Johnson, Boulder, members of the Executive Committee. An invitation from President Edward Eyring, New Mexico Highlands University, to meet in Las Vegas, New Mexico, in 1948 was accepted. A second Alpine Texas meeting for 1949 was also approved following invitations from President R. M. Hawkins, of Sul Ross State College, and Otto Struve, honorary director, McDonald Observatory. The 1949 meeting will be especially interesting, since various societies in Chihuahua, Mexico, have joined in the invitation and assured us of their cooperation, offering to serve as hosts for an excursion into Old Mexico after the formal sessions. The first Alpine meeting was held in 1939 on the occasion of the dedication of the McDonald Observatory on Mt. Locke, at which time both the college and the observatory served as hosts.

At the conclusion of the meeting guests joined excursions offered to study "The Geology of the Pikes Peak Region," "The Manitou Experimental Forest," or "The Watersheds East and North of Colorado Springs." (FRANK E. E. GERMANN, Executive Secretary-Treasurer, Southwestern Division.)

Meeting of Pacific Division

The 28th annual meeting of the Pacific Division, AAAS, was held in San Diego, California, June 16–21, 1947, with 970 registered members and guests in attendance. This, the second San Diego meeting of the Division, was held at the invitation of the San Diego Council of Technical and Scientific Societies, Society of Natural History, State College, and Zoological Society, the Scripps Institution of Oceanography, the U. S. Navy Electronics Laboratory, and 11 other scientific and technical organizations and institutions in the area. Headquarters were established at the U. S. Grant Hotel, and meetings were held there and at the San Diego Hotel, in the Chamber of Commerce Auditorium, at San Diego State College, and in church and school auditoriums.

The general sessions began on the afternoon of June 16 with a symposium on "The Pacific Basin." K. O. Emery spoke on "The Submarine Geology of Bikini Atoll," H. U. Sverdrup took as his topic "Oceanography and Meteorology." and J. L. Kask discussed economic and international aspects of the Pacific fisheries under the title "Who Harvests the Pacific?"

At 4:30 P.M. a reception for members of the Association and associated societies and their guests was held in the Palm Court of the U. S. Grant Hotel.

The symposium on "The Pacific Basin"

was continued on Tuesday morning with papers by E. B. Copeland, on "Origin of the Native Flora of the Pacific Islands"; R. L. Usinger, on "Wartime Dispersal of Pacific Island Insects"; and F. W. Hartmann, on "Public Health Problems in the Pacific Islands." At the conclusion of the Tuesday morning session, Chairman K. A. Ryerson, of the Pacific Science Board, reviewed the plans of the Board for the promotion and coordination of research in the Pacific area, especially in the islands taken over by the United States during the war.

The address of T. G. Thompson, retiring president of the Pacific Division, was given Tuesday evening on the topic "Research." Prof. Thompson spoke particularly of the importance of research to the national defense and of the need of a more comprehensive plan for the mobilization of scientific talent and scientific resources.

On Wednesday evening L. A. DuBridge, president, California Institute of Technology, dealt with the reciprocal of this theme in a lecture on "Radar and Its Peacetime Uses."

The concluding evening address was given Thursday by G. L. Clarke, of Harvard University and the Woods Hole Oceanographic Institution, on "Light and Life Within the Sea."

Roy E. Clausen, of the University of California, Berkeley, was elected to the presidency of the Division, succeeding Prof. Thompson. H. S. Reed continues as vice-president and chairman of the Executive Committee. R. C. Miller was reelected secretary for a three-year term. W. A. Clemens was elected a member of the Executive Committee for a five-year term, and W. Weniger and G. E. Goodspeed, members-at-large of the Council for four-year terms.

A resolution was adopted endorsing the Fulbright Law (*Science*, May 9, p. 483) and urging that, in view of the predominant interest of other countries and governments in science and the value of scientific relations in building world peace, at least three of the 10 appointees to the Board of Foreign Scholarships be men prominent in the natural sciences. This resolution was telegraphed to the President of the United States. A further resolution was adopted urging the removal of all restrictions on exchange of scientific publications between the United States and Japan.

A resolution was adopted expressing to the local committee and the host institutions and organizations the appreciation of the officers and members of the Pacific Division and associated societies of the excellence of the facilities provided and the cordial hospitality extended this scientific gathering.

Three additional organizations, the Herpetologists League, the Meteoritical Society, and the Oregon Academy of Science, were elected to the status of associated societies of the Division.

The following societies meeting in conjunction with the Pacific Division held programs for the reading of scientific papers: American Chemical Society (Pacific Intersectional Division), American Meteorological Society, American Phytopathological Society (Pacific Division), American Society for Horticultural Science (Western Section), American Society of Ichthyologists and Herpetologists (Western Division), American Society of Plant Physiologists (Western Section), Association of Pacific Coast Geographers, Astronomical Society of the Pacific, Botanical Society of America (Pacific Division), Ecological Society of America (Western Section), Herpetologists League, Institute of Mathematical Statistics, Meteoritical Society, National Science Teachers Association (Western Area), Oceanographic Society of the Pacific, Society of American Bacteriologists (Southern California Branch), Society for Experimental Biology and Medicine (Pacific Coast Branch and Southern California Branch), Western Psychological Association, Western Society of Naturalists, and Western Society of Soil Science.

Action was taken to accept the invitation of the University of California to hold the next annual meeting of the Division on the Berkeley campus, June 21–26, 1948. (ROBERT C. MILLER, Secretary, Pacific Division.)

Advance Registration and Hotel Headquarters Assignments

Those planning to attend the Chicago Meeting of the AAAS, December 26–31, may register now by sending the correct fee ($2.00 for members and college students, $3.00 for nonmembers) to the Washington Office of the Association, 1515 Massachusetts Avenue, N.W. Those registering before December 1 will receive a copy of the *General Program* well in advance of the meeting, will save themselves the time of registering during the meeting, and will have their names included in the special directory of registrants which will be available for inspection in all the headquarters hotels.

The *General Program* will list the papers of the sections and societies meeting with the Association, including the time and place of each session. It will also contain announcements regarding general sessions, the International Science Exhibition, eating facilities, transportation, mail and messenger service, and a directory of speakers and presiding officers. Readers will find the Summary of Sessions a most useful adjunct.

Registration fees will be accepted for mail distribution of the *General Program* until December 10. Payments received after this date will be held and placed on file on December 26 at the main registration center, located adjacent to the Exhibition in the Stevens Hotel. Upon identification, these registrants will be given a copy of the *General Program*, and their registration cards will be placed in the Visible Directory. To avoid delay in receipt of copies of the program during the Christmas mailing rush, registration fees should reach the Washington Office before December 1.

Scientific Exhibits

Plans for many fine scientific exhibits demonstrating research progress and techniques in varied fields are progressing rapidly. A special exhibit being prepared by a group of the 1946 Nobel Prize winners will show the research for which each scientist was honored. Other exhibits scheduled include: "Radar Charting on the Ohio River," prepared by the Louisville Engineer District Corps of Engineers, U.S.A.; "Magnetic Expiration in the Antarctic and Arctic Alaska," by the Division of Electricity and Magnetism, Naval Ordnance Laboratory; "Hydrocarbon Research and Electronic Miniaturization," by the National Bureau of Standards; "Progress in the Art of Prosthetic Devices," by the Veterans Administration; "Bulbar Poliomyelitis and Epidemiology and Diagnosis of Infantile Paralysis," by the National Foundation for Infantile Paralysis; and "Anatomic Specimens Embedded in Plastics," by Otto F. Kampmeier, University of Illinois College of Medicine.

Arrangements for technical exhibits by a large number of commercial organizations have already been made since the first announcement in *Science*.

NEWS
and Notes

Loren C. Eiseley, head, Department of Sociology and Anthropology, Oberlin College, Oberlin, Ohio, has resigned to become professor of anthropology and chairman, Department of Anthropology, University of Pennsylvania.

Charles H. Brown, director of the Iowa State College Library for 24 years, has recently been honored by the Association of College and Reference Libraries. A special July edition of the Association's publication, *College and Research Libraries,* contains papers assembled as "a testimony to the energy and productiveness of one of America's outstanding librarians." Under his direction the Library grew from 90,000 volumes, scattered about the campus, to a 370,000-volume centralized institution. An article on scientific publishing in Europe, which reflects Dr. Brown's interest in library cooperation and rehabilitation both here and abroad, appeared in the July 18 issue of *Science.*

Salvatore P. Lucia, associate professor of medicine and chairman, Subdivision of Preventive Medicine, University of California Medical School, has been promoted to full professor of medicine.

Walter C. Russell, executive secretary, Graduate Faculty, and professor of agricultural biochemistry, Rutgers University, was awarded the honorary D.Sc. degree by Ohio Wesleyan at its recent commencement.

James F. Ferry, West Virginia University, has been appointed associate professor of botany, Louisiana Polytechnic Institute.

William F. Hughes, Jr., former associate at Indiana University, has been named professor and head, Department of Ophthalmology, University of Illinois College of Medicine, Chicago.

Alan Andrew, teaching assistant and former research staff member of the rocket project at California Institute of Technology, has been named assistant professor of physics at Pomona College, Claremont, California, for the coming year.

Rupert Wildt, assistant professor of astrophysics, Yale University, and **Donald H. Menzel,** professor of astrophysics, Harvard University, have been invited to attend a conference on "The Relations Between Solar Phenomenon and Geophysics" at Lyon, France, September 1–7. This is one of a series of international scientific meetings being organized by the French National Center of Scientific Research with the aid of the Rockefeller Foundation.

Oscar Riddle, Carnegie Institution, retired, has been elected to honorary membership in the Physiological Society of India and in the Facultades de Medicina, Farmacia y Química, San Carlos University, Guatemala, and to fellowship in the Sociedad Mexicana de Historia Natural.

C. M. Louttit, who recently resigned as dean of faculty, Sampson College, has been appointed professor of psychology and dean, Undergraduate Division, University of Illinois, Galesburg.

Hans G. Schlumberger, Western Reserve Medical School, has been appointed to the staff, Department of Pathology, Ohio State University, where he will investigate cancer in animals, particularly fish and frogs, and study the transmissibility of the disease and cancer cell growth in these animals.

Howard J. Curtis, associate professor of physiology, College of Physicians and Surgeons, Columbia University, has been appointed head, Department of Physiology, Vanderbilt University School of Medicine, succeeding **Glenn A. Millikan.** During the war, Dr. Curtis served as director of biological research at Oak Ridge, Tennessee.

Leslie E. Card, professor of poultry husbandry, University of Illinois College of Agriculture, has been named head of the Department of Animal Science (formerly Animal Husbandry), succeeding **William E. Carroll,** who has been appointed associate director of the Agricultural Experiment Station.

Visitors to U. S.

Louis Van den Berghe, Institute of Tropical Medicine, Antwerp, Belgium, and a member of the staff, Institute for Scientific Research in Central Africa, was a recent visitor at the University of Texas Medical Branch, Galveston, for a conference on chemotherapy of tropical diseases, at which he reported on the use of Bayer 205 in certain filarial infections. Dr. Van den Berghe has also visited the University of California Medical Center, San Francisco, and other American institutions interested in tropical medicine.

C. F. Robinow, British pioneer in the study of bacterial cytology, and at present in charge of a research project of the Welcome Foundation at Strangeways Laboratories, Cambridge University, will be visiting professor at Indiana University for the second semester of 1947–48.

Aage Jepson, professor of bacteriology, Royal Veterinary College, Copenhagen, Denmark, is on special leave in this country for the purpose of becoming acquainted with faculties and curricula of veterinary colleges, officers of the American Veterinary Medical Association, and regulatory officers in charge of food production and storage and dairy hygiene. Dr. Jepson has already visited several dairy, creamery, food production, and freezer plants as well as packing houses in this country.

M. Désirant, of Liége University, Belgium, who has been working recently at the R. S. Mond Laboratory, Cambridge, England, will arrive in September for a visit to various cryogenic laboratories and for a prolonged stay at Massachusetts Institute of Technology and the National Bureau of Standards.

Grants and Awards

Grants amounting to $181,044, recently authorized by the Sugar Research Foundation, Inc., bring the total allotted by the Foundation for grants-in-aid and special studies to $534,160. The appropriations provide for the continuation of 26 established projects and the initiation of four new investigations: (1) nutritional value of sugar cane juice and studies of the physiology of sucrose and levulose, by Tomas Duran-Quevedo, University of Havana; (2) a study of clay adsorption methods for removing sugar from molasses and commercial applicability of this technique, by L. K. Herndon, Ohio State University; (3) research on special fuels and heating units using sugar, by Frederic S. Bacon Laboratories, Watertown, Massachusetts; and (4) a study of

production of lactic acid from molasses and its recovery in a pure state, by the Bjorksten Research Laboratories, Chicago.

George F. Cahill and **Meyer M. Melicow**, both of the Squier Urological Clinic, Presbyterian Hospital, Columbia University, were awarded a gold medal at the Centenary Convention of the American Medical Association, held recently in Atlantic City, for their exhibit on "Tumors of the Adrenal Gland." They also received first prize for the same exhibit at the American Urological Convention in Buffalo.

A grant of $1,500 has been made by the U. S. Vitamin Corporation, New York City, to the Department of Dermatology, New York University College of Medicine, for research in diseases of the skin associated with vitamin deficiencies.

Industrial Laboratories

A. C. Krueger, formerly development engineer, Guided Missiles Project, Republic Aviation Corporation, and during the war with the Manhattan Project, University of Chicago, has been appointed supervising engineer, Antenna Design Section, Airborne Instruments Laboratory, Inc., Mineola, New York. His assumption of administrative direction of the Section, permits **R. S. Wehner,** co-supervisor, to take an active part in the research and development activities of the group. The Section is developing faired-in, dragless antennas for transsonic and super-sonic aircraft.

W. Harry Feinstone, director, Biological Research, Pyridium Corporation, has been appointed director of research and development, Central Pharmacal Company, Seymour, Indiana.

Frederic H. Lahee, chief geologist for Sun Oil Company since 1920, has been appointed geological and research counselor of the Production Department. As such, he will be available for consultation on all matters of production science throughout the Company.

Centro Research Laboratories, Inc., is offering a Standard Test Service, which will be of special interest to activities and industries associated with paint, varnish, lacquer, resin, pigment, drug, chemical, oil, soap, lubricant, insecticide, fungicide, electrical insulation, textile treating, paper and pulp finishing. Costs are adjusted to the type of test and the number of samples to be processed simultaneously. Further details may be obtained from the Technical Service Director, Centro Research Laboratories, Inc., Briarcliff Manor, New York.

Eli Lilly and Company Research Laboratories made several organizational changes on July 1. New department heads include **James W. Ferguson,** Organic Chemical Development Process; **Carter C. Boyd,** Chemical Manufacturing Process; **Robert D. Rock,** Chemical Manufacturing Equipment; **Gail L. Shaw,** Organic Chemical Development Equipment; and **Harold K. Leamon,** Organic Chemical Manufacturing.

Hendrik M. Rozendaal, physician, Schenectady, New York, has been appointed to the staff, General Electric Research Laboratory, Schenectady, to serve as liaison representative between the Laboratory and the various groups working in biological research in the field of atomic energy.

Josselyn Farmer, who recently obtained her Ph.D. in organic chemistry from the University of Cincinnati, has been appointed assistant librarian of The Wm. S. Merrell Company, Cincinnati, Ohio.

Ernest B. Benger, research chemist and manager, Rayon Technical Division, Du Pont Company, retired on June 25 after 30 years of service.

Colleges and Universities

Northwestern University's University College and Department of Chemistry, College of Liberal Arts, are sponsoring a series of lectures on "The Chemistry and Physics of High Polymers," to be given every Tuesday evening from September 30 to December 9 in Lincoln Hall, East Chicago Avenue, Chicago. The lectures will constitute a noncredit course and are open only to those who have paid the usual course fee. Lecturers in order of date will be H. Mark, Brooklyn Polytechnic Institute; E. F. Izard, DuPont Company, Buffalo; H. A. Bruson, Resinous Products and Chemical Company, Philadelphia; E. G. Rochow, General Electric Company, Schenectady; R. B. Woodward, Harvard University; W. O. Baker, Bell Telephone Laboratories; P. Debye, Cornell University; Malcolm Dole, Northwestern University; P. J. Flory, Goodyear Research Laboratory, Akron; A. V. Tobolsky, Princeton University; and F. R. Mayo, U. S. Rubber Company, Passaic.

Michigan State College has announced the following appointments in the Department of Chemistry: Robert M. Herbst, E. Bilhuber-Knoll Corporation, associate professor of organic chemistry; **Frederic S. Dutton,** Baldwin-Wallace College, associate professor in charge of general chemistry; and **Robert D. Schuetz,** Ohio State University, and **Kenneth G. Stone,** Sun Chemical Company, instructors.

The University of Cincinnati has planned an Institute of Industrial Health which will offer a two-year, highly specialized program of graduate study and training in the field of industrial medicine leading to the new degree of Doctor of Industrial Medicine. Robert A. Kehoe, director, Kettering Laboratory of Applied Physiology at the University, will direct the new Institute. Requirements for admission will be unusually high, and those accepted will be limited in number.

Meetings

The Society of General Physiologists will hold its annual meeting September 8–9 at Woods Hole, Massachusetts. Programs dealing with transport of ions across cell membranes, cellular metabolism, and other topics in general physiology have been arranged. Accommodations are available at the Marine Biological Laboratory for those who attend the meeting. Reservations should be made directly with the Laboratory.

The Administrative Section on Medical and Allied Professional Sciences of the Association of Military Surgeons will meet at the Hotel Statler, Boston, on November 13–15, inclusive. All officers of the Medical Administrative Corps, Pharmacy Corps, and Sanitary Corps who plan to attend the meeting at Boston are asked to communicate with Major A. E. A. Hudson, SnC, president of the Section, Apt. 1-4, Edgewood Apartments, Goldsboro, North Carolina.

A High-Vacuum Symposium, sponsored by the National Research Corporation in cooperation with the Division of Industrial and Engineering Chemistry, American Chemical Society, will be held at the Hotel Commander, Cambridge

Massachusetts, October 30-31. Attendance will be restricted to technical and scientific personnel concerned with industrial applications of high vacuum.

A Conference on Motor Skills Research, held at the Special Devices Center, Office of Naval Research, Sands Point, New York, June 26–27, was attended by 40 scientists representing some 20 organizations both within and outside the services. Leonard C. Mead, head, Human Engineering Section, Special Devices Center, was chairman of the General Session; Glen Finch, Aero-Medical Laboratory, Wright Field, of the session covering reports on Current and Planned Research on Motor Skills; and J. W. Macmillan, Medical Sciences Division, ONR, of the session on Psychomotor Research in Relation to Military Problems. An open discussion on topics relating to psychomotor research was also led by Leonard Mead.

The State Geologists of Illinois, Iowa, Kansas, Nebraska, and South Dakota, accompanied by staff members and scientific guests, held a field conference on the loess deposits of the upper Mississippi valley region and related problems, June 21–28, inclusive.

The Midwest Field Conference began at the classic Farm Creek section near Peoria, Illinois, continuing along the belt of thick Illinois valley loess east of Havana and Beardstown, Illinois, through western Illinois to southeastern Iowa on the Illinoian drift plain, thence to the loess deposits bordering the Iowan drift plain near Iowa City, westerly along the southern border of the Iowan drift to the Des Moines lobe (Mankato substage), thence to the Iowan drift area of northwestern Iowa and the adjacent Kansan drift, on to the Dakota lobe in southeastern South Dakota, and finally southward through eastern Nebraska to Lincoln, along a traverse that showed a large part of the interesting Pleistocene section of that state.

Those attending *from Illinois* were M. M. Leighton, chief, and H. B. Willman, head, Division of Areal Geology and Paleontology, Illinois Geological Survey, Urbana; *from Iowa*, A. C. Trowbridge, head, Department of Geology, University of Iowa, H. Garland Hershey, state geologist, and Stanley Harris, geologist, Iowa Geological Survey, all of Iowa City; *from Kansas*, R. C. Moore, state geologist and professor of geology, John C. Frye, executive director, State Geological Survey, and professor of geology, and A. Byron Leonard, professor of zoology, all of the University of Kansas, Lawrence; *from Nebraska*, G. E. Condra, dean and chief, Conservation and Survey Division, and state geologist, Eugene C. Reed, associate state geologist, Eck F. Schramm, professor and head, Department of Geology, Alvin Lugn, professor of geology, Mylan Stout, professor of geology, C. Bertrand Schultz, director, State Museum, and Weldon D. Frankforter, assistant curator of Paleontology, State Museum, all of the University of Nebraska, Lincoln, and Gilbert Lueninghoener, professor of geology, Fremont College, Fremont; *from South Dakota*, E. P. Rothrock, state geologist and head, Department of Geology, and Bruno Petsch and Bruce Baldwin, of the University of South Dakota, Vermillion; *from Federal departments and other institutions*, Arthur D. Howard, U. S. Geological Survey, Washington, D. C., Richard F. Flint and Dwight Crandall, U. S. Geological Survey and Yale University, Guy D. Smith, U. S. Department of Agriculture, Ames, Iowa, and William T. Watkins, U. S. Department of Agriculture, Lincoln, Nebraska.

NRC News

With the ending of the war, the unique and highly successful relationship which existed between the Federal Medical Departments and the Medical Advisory Committees of the NRC was to cease, the mission of the committees having been fulfilled. It was clearly evident, however, that the maintenance of professional relationships between the Federal departments and the NRC was still needed in connection with many problems arising in the Armed Forces, the Veterans Administration, and other government agencies. As the date drew near for the dissolution of the wartime committees, impetus for the continuation of the advisory mechanism in the postwar period came from the Surgeon General of the Army. In March 1946, Major Gen. Norman T. Kirk proposed to the president of the National Academy of Sciences that steps be taken to provide continuing cooperation. As a result, a tripartite contract was executed between the Medical Departments of the Army, Navy, and Veterans Administration for financial support of the work. Thus, the collaboration that existed during the war years has been extended.

Since dissolution of the wartime committees in June 1946, new committees have been formed as follows: Committee on Atomic Casualties; Committee on Aviation Medicine: Committee on Chemotherapy; Committee on Hearing; Committee on Medicine, including Subcommittees on Cardiovascular Diseases, Infectious Diseases, Liver Diseases, Tropical Medicine, Tuberculosis, and Venereal Diseases; Committee on Neuropsychiatry; Committee on Pathology; Committee on Sanitary Engineering, including a Subcommittee on Military Water Treatment; Committee on Surgery, including Subcommittees on Anesthesia, Neurosurgery, Ophthalmology, Orthopedic Surgery, Thoracic Surgery, and Vascular Surgery.

Members of the newly-constituted committees were chosen on the basis of their medical and scientific leadership and, since many of the members served in the Medical Departments of the Army and Navy, they have an intimate understanding and appreciation of the problems on which the representatives of the Federal departments desire advice. The questions are carefully and broadly analyzed in open discussion, and if recommendations can be made promptly, these are formulated and forwarded to the department concerned. If there is need for further study and consultation, such problems are assigned to panels within the committee, the chairman of which reports back at the next meeting.

Since the formation of the committees, advice has been sought by the Federal services on a wide variety of problems. One of these—revision of Army and Navy physical standards—will be a major continuing interest of the Committees on Medicine, Surgery, and Neuropsychiatry. Each phase of the physical standards will be critically reviewed by competent specialists who will evaluate physical and mental requirements in relation to job placement. It is believed that this approach to the selection of personnel will enable the services to utilize individuals heretofore considered physically disqualified in assignments wherein effective service may be rendered and may help to prevent great losses of man power such as occurred during the last war. Although many phases of the standards can be revised on the basis of existing knowledge, some may require extensive research on the part of the committees.

The nature and scope of the problems placed before the Medical Advisory Com-

mittees by the Federal services are revealed by the following list: (1) evaluation of auditory requirements for admission to the U. S. Military Academy and of research projects in the broad field of audition; (2) evaluation of research on rheumatic fever; (3) evaluation of a study of intracutaneous influenza vaccination; (4) evaluation of penicillin prophylaxis of venereal diseases; (5) establishment of policies regarding the insurability of syphilitic patients; (6) establishment of policies regarding the use of contact lenses and the supply of anesthetic ophthalmic ointments; (7) evaluation of BCG as a prophylactic measure against tuberculosis; (8) evaluation of research projects on epilepsy and other neuropsychiatric disorders; (9) evaluation of vision tests; (10) evaluation of various projects in the field of sanitary engineering.

In addition to the meetings of the Medical Advisory Committees, conferences have been sponsored under their auspices on peripheral nerve injuries, penicillin prophylaxis of venereal diseases, streptomycin therapy of tuberculosis, and recent advances in aviation medicine.

An active interest has also been taken in the promotion of research within the Federal Medical Departments. In cooperation with the Committee on Veterans' Medical Problems, proposals have been made for clinical studies of conditions which arose during the war, including extensive studies in medicine, surgery, and neuropsychiatry. Among the studies currently under consideration are: a follow-up study of peripheral nerve injuries, investigation of the late results following repair of arterial aneurysms and arteriovenous fistulae, liver function in veterans following hepatitis and other conditions. The committees also serve in an advisory capacity in connection with research proposals originating in the Army, Navy, and Veterans Administration. They thus exercise an important influence upon federally-sponsored research in medicine and allied fields.

The Chemotherapy Center for Tropical Diseases is continuing its work, though on a reduced scale, since demands for drugs required for the cure and prevention of various tropical infections are no longer urgent. Under the direction of the Center, pharmacologic and toxicologic tests have been carried out on a variety of drugs that may be effective in the treatment of amebiasis, leshmaniasis, schistosomiasis, and other infections.

As the newly-constituted Medical Advisory Committees near the end of their first year of activity, it may be said that their work may prove equally far-reaching, if less dramatic, than that of their wartime counterparts. Certainly, the knowledge and experience of the civilian physicians on the committees, as it is brought to bear on the medical problems of the Army, Navy, and Veterans Administration, will go a long way toward the maintenance of high professional standards in the Federal medical services. The work of the committees will also have an important bearing upon the Nation's medical preparedness.

An international journal, *Spectrochimica Acta*, the publication of which was begun in 1939 by Julius Springer, Berlin, and interrupted shortly afterward by the war, has been re-established as an international organ for spectroscopists and spectrochemists, and is being published in the Vatican under the editorship of Alois Gatterer, assisted by a group of coworkers from other countries, as follows: R. Breckpot (Belgium), H. Kaiser (Germany), E. Van Someren (England), and Lester W. Strock (United States). The first number (No. 1, Vol. 3) is now ready for press, and it is expected that 6–8 numbers a year will be issued. The official languages of the journal are English, French, and German; papers will also be accepted in both Italian and Spanish. Papers in English from this country should be submitted to Lester W. Strock, 21 Madison Avenue, Saratoga Springs, New York.

The U. S. Civil Service Commission has announced probational employment opportunities as Technical Editor, at salaries ranging from $3,397 to $5,905 per year; as Director, Technical Information, at $7,102 per year; and as Writer (Military Manual), at $4,140 per year. Vacancies are located at the Army Chemical Center, Maryland. Competitors for these positions will not be required to take a written test. Further information concerning these openings may be obtained at most post offices, and forms may be obtained from the Executive Secretary, Board of U. S. Civil Service Examiners, Army Chemical Center, Maryland, or from the Director, Fourth U. S. Civil Service Region, Nissen Building, Winston-Salem 3, North Carolina. Applications will not be accepted after September 8.

A long-range program of research on waterproofed papers is under way at the National Bureau of Standards under a fellowship of the Waterproof Paper Manufacturers Association. Robert C. Reichel, whose services are being provided by the Association, is acting as research associate. Laboratory facilities and technical assistance are furnished by the Bureau. Current work involves the development of a suitable accelerated aging test for predicting permanence of a wide variety of papers. Tests for measuring changes in their properties when exposed to deteriorating influences will be undertaken. Other projects will include means of reducing their flammability, relation of properties of waterproofing asphalts to performance of the papers, and odor and taste problems in food packaging.

The Rockefeller Institute for Medical Research plans to consolidate all phases of its program on its York Avenue site in New York City. The integration in New York of the Department of Animal and Plant Pathology with the Departments of the Laboratories and the Hospital has recently been approved. Most of the activities at the Institute at Princeton will be transferred to the New York plant with the belief that they will be greatly strengthened by making possible a day-to-day exchange of ideas between the members of the entire scientific staff. It is hoped that this integration may be accomplished by July 1, 1951.

Make Plans for—

American Astronomical Society, 77th meeting, September 3–6, Dearborn Observatory, Evanston, Illinois.

First International Biometric Conference, September 5–6, Marine Biological Laboratory, Woods Hole, Massachusetts.

Laurentian Hormone Conference of the AAAS, September 8–13, Ste. Adele Lodge, Ste. Adele, Quebec.

American Psychological Association, September 9–13, Detroit, Michigan.

American Association for the Advancement of Science, 114th Meeting, December 26–31, Chicago, Illinois.

TECHNICAL PAPERS

Calcium and Growth in Aging and Cancer[1]

ALBERT I. LANSING

Department of Anatomy, Washington University School of Medicine, and *Barnard Free Skin and Cancer Hospital, St. Louis*

This paper is an attempt to bring together data on changes in intracellular calcium as an important factor in both aging and malignancy. A calcium increase with age has been demonstrated in a wide variety of organisms by many investigators, some of whom are Novi (*20*), Cahane (*5*), Burger and Schlomka (*4*), Simms and Stolman (*22*), Lansing (*12, 13*), and Blumenthal, Lansing, and Wheeler (*2*).

Between the cells calcium is increased in some locations and even decreased in others. It is with the cells themselves that we are concerned, both in aging and in cancer production. Lansing (*12, 13*) noted a marked increase with age in the calcium content of the cell periphery or cortex. This was demonstrated in a plant, a rotifer, a planarian, and a toad. At that time it was suggested that an increase with age in the calcium content of the cell cortex might produce a decrease in permeability of the cell membrane. It was further suggested that a permeability decrease might result in an accumulation of metabolic waste products in the cell which could, in turn, produce the changes associated with senescence.

This view is not without support. Benedict (*1*), as a result of his permeability studies in plants, suggested that aging is a result of decreased cellular permeability. Molisch (*17*) believed that there might be a relation between a calcium increase and a permeability decrease with age in plants. That senescence may be a consequence of progressive accumulation in the cell of materials which either are toxic or obstruct metabolism has been frequently suggested (Jickeli, *10*; Montgomery, *18*; Child, *6*; Seifriz, *21*; and Heilbrunn, *9*).

A series of experiments were conducted by the writer to determine the effect of experimental alteration of the calcium content of cells on longevity (*14*). It was found that, under carefully standardized environmental, nutritive, and genetic conditions, rotifers in a low calcium medium live longer than control animals. It was further shown that experimental removal of calcium from cells of the rotifer by sodium citrate results in a marked increase in longevity. The ability of sodium citrate to remove calcium from the cell cortex was demonstrated by microincineration and electron microscopy (*16*).

The mechanism of aging as set forth is obviously incomplete in that a serious gap exists in the postulated chain of events. Why does calcium increase with age in the cell cortex? This discussion of experiments on longevity and chemical studies on cancer may make it possible to relate the calcium change with age to a mechanism governing growth cessation of cells.

The results of a wide variety of experiments on the effect of starvation on longevity are in essential agreement that starvation increases longevity by extension of the period of growth. Northrop (*19*), in his experiments on *Drosophila*, showed that semistarvation resulted in increased total duration of life. Increased longevity was due to a prolongation of the period of growth; length of the adult period of life was unaffected. Similarly, Kopec (*11*), working with *Lymantria*, *Drosophila*, and tadpoles concluded that prolongation of total duration of life is effected by an extension of the period of growth and that the adult period is not increased. Comparable results with rats have been obtained by McCay and his associates in an extensive series of investigations (*8*). It would appear from these and similar experiments that the length of the period of growth may condition longevity and that cessation of growth may set off the aging mechanism.

Recent experiments by Lansing (*15*) and current unpublished data indicate that cessation of growth is, in fact, a critical turning point in initiation of age changes. Use was made of standardized nutritive and environmental conditions and genetically homozygous rotifers with parental age as the sole variable. Longevity of successive generations of rotifers was traced, parental age being uniformly maintained and lines of young and old parentage contrasted. Lines of old parentage showed progressive decline in mean life span, and all became extinct after a limited number of generations. However, lines of young parentage maintained and increased mean life spans.

Significant in the present discussion is the observation that there is a sharply defined transition between ages of lines that maintain and increase longevity or progressively reduce it. Lines of a parental age younger than that at which growth ceases show progressively increased longevity and are evidently free of any age change. *All* lines of parental age older than that at which growth ceases show progressive reduction of mean life spans to the point of nonviability. The conclusion is warranted that the process of aging is a consequence of changes which occur with cessation of growth.

If cessation of growth is a significant factor in aging and if a mechanism involving calcium increase is an integral part of this system, one would expect to find the very opposite situation in cancer. Cancer may be regarded as a very youthful and vigorous tissue with tremendous and uncontrolled growth capacity.

It has been shown repeatedly that cancer tissue is markedly low in calcium. Recently, Suntzeff and Carruthers (*23*) have shown that there is a 50 per cent reduction of total calcium in methylcholanthrene-induced epidermal hyperplasia from that of normal epidermis, and in squamous cell carcinoma a still further reduction of approximately 60 per cent from the precancerous hyperplastic epidermis. Brunschwig, Dunham, and Nichols (*3*) also discovered a sharp drop of calcium in cancer tissue.

In an extension of the observations of Suntzeff and Carruthers, Lansing, Rosenthal, and Au (to be published) studied the nature of the calcium drops in hyperplastic mouse epidermis and resulting carcinomas by means of ultrafiltration.

[1] Supported in part by grants from the Josiah Macy, Jr. Foundation.

It was found that the ultrafilterable calcium fraction of a squamous cell carcinoma was sharply reduced on both an absolute and relative basis. The conclusion was reached that the base-binding capacity of an organic fraction which binds calcium is altered in cancer. It is reasonable to expect that this calcium binding complex, which changes in cancer to limit calcium uptake, is located like that demonstrated by Heilbrunn in the cell cortex. The work of Heilbrunn and his associates, covering a number of years, are summarized in his book (*9*).

Further supportive but indirect evidence for the localization of the calcium change in cancer in the cell surface can be found in the work of Coman (*7*), who has found that normal cells are more readily separated by micromanipulation when in calcium-free medium than when in balanced salt solution. Further, he has demonstrated that cancer cells are more readily separated than are normal cells, and the suggestion was made that the decreased adhesiveness of cancer cells results from a local calcium deficiency which facilitates separation of these cells from one another.

Thus, the evidence presented, while undoubtedly weak, makes it possible to correlate the various changes described in a single hypothesis. It seems quite likely that an organic calcium-binding complex of the cell cortex plays an integral part in the growth regulatory mechanism of cells and that at the time of cessation of growth this calcium-binding complex, presumably a protein, is altered or reoriented in such a way as to increase calcium-binding capacity. Thus, a mechanism is offered which at least in a general way synchronizes the changes that occur with age. On the other hand, when the calcium-binding system alters in such a manner as to decrease calcium binding, growth does not cease, age changes do not occur, and, in effect, the state of affairs exists that is associated with cancer. This hypothesis is also compatible with Coman's concept of the invasiveness of cancer.

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Coproantibody Excretion During Enteric Infections[1]

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The immune mechanism responsible for initiation of recovery from infections confined essentially to the lumen and mucosa of the intestinal tract, viz., cholera, bacillary dysentery, and certain *Salmonella* infections, is suggested by the recent work of Burrows and co-workers (*1*), who showed that antibody is excreted in the feces by both infected and immunized animals and immunized human volunteers, and that immunity to experimental infection is associated with its presence. They showed that the appearance of coproantibody precedes that of serum antibody, reaches peak titer and declines while serum antibody is still rising, and completely disappears despite the persistence of serum antibody. They suggested that the independent behavior of serum and fecal antibody might be explained on the assumption that the latter represents intracellular antibody, possibly transported to the lumen of the bowel by lymphocytes. However this may be, the late appearance and persistence of serum antibody strictly limits its diagnostic utility, but the behavior of coproantibody suggests that it might be useful both in the rapid diagnosis of specific acute enteric infection and in providing a clue to the possible etiology of chronic diarrheal disease such as chronic ulcerative colitis.

TABLE 1

Coproantibody Excretion From Patients Suffering From a Variety of Enteric Infections

Clinical diagnosis	No. cases	Pathogens isolated	Coproantibody present
Acute bacillary dysentery	20	*S. sonnei* from 6; *S. flexneri* from 5; none from 9	20*
Chronic bacillary dysentery	18	*S. sonnei* from 3; *S. flexneri* from 5; none from 10	18†
Acute diarrhea	14	Various *Salmonella* from 10; none from 4	14†
Chronic diarrhea	35	Para A from 9; Para B from 3; none from 23	32‡
Chronic ulcerative colitis	5	*S. flexneri* from 1; *S. sonnei* from 2; none from 2	5§

* Eleven, 1:640 or above; 8, 1:320; 1, 1:160 (maximum titers obtained).

† Coproantibody titer of 1:160 or above obtained against homologous organism, or against one or more species of enteric pathogens, on several occasions from each patient.

‡ Three failed to show coproantibody at any time during the observation period.

§ Usually obtained in highest titer during episode of exacerbation of disease.

[1] Aided in part by a grant from the M. D. Anderson Foundation of Houston.

[2] The authors are indebted to William Burrows for making available copies of translations from the Russian (*4*) furnished him by the Translation Unit of the U. S. Public Health Service.

Although we were unaware of previous reports of the presence of fecal antibody in dysenteric stools at the time this work was initiated, it was of some interest to find that Davies (*2*) earlier had demonstrated antibody in dysenteric stools and suggested use of serological examination of feces for rapid diagnosis of acute bacillary dysentery. More recently, Soviet investigators (*4*) have utilized fecal antibody titration in early diagnosis of bacillary dysentery.

The present report is concerned with some observations on the presence of antibody in fecal specimens from patients with a variety of enteric infections. The method of preparation of fecal specimens was essentially that used by Burrows (*1*). Agglutinin titration was carried out in the usual manner. Examinations were made at frequent intervals during active infection and convalescence and, in some instances, over a period of several months. Serum and fecal agglutinin titrations were carried out simultaneously with stool cultures.

Table 1 summarizes the results. The grouping of patients was based on the clinical diagnosis, isolation of enteric pathogen, and presence of fecal agglutinins for the particular infectious agents indicated. Although positive cultures were obtained from only 47.8 per cent of the patients included in the table, it is of some interest that fecal agglutinins were found in 96.7 per cent of the cases. Thus, of 20 cases of acute bacillary dysentery and 18 of chronic bacillary dysentery, all showed fecal agglutinins of significantly high titer; likewise, of 14 cases of acute diarrhea and 35 of chronic diarrhea, most of the fecal specimens contained high-titer agglutinins. Three in the latter series failed to show coproantibody at any time during the observation period. Five cases of chronic ulcerative colitis were studied; fecal agglutinins were demonstrable in high titer in all cases during one or more episodes of exacerbation of the disease.

Fig. 1 illustrates the typical serum and fecal agglutinin response observed in acute bacillary dysentery. Fecal agglutinins were demonstrable as early as the 3rd day of disease, rose to high titer by the 9th day, and disappeared soon after stool cultures became negative and after recovery definitely was established. On the other hand, circulating antibody did not appear to significant titer until about the time recovery was initiated, but then rose to high titer and remained at a high level during the period of observation.

In cases of chronic bacillary dysentery significant fecal agglutinin titers were obtained on several occasions from each patient during the period of examination. Acute diarrhea of *Salmonella* origin followed the fecal antibody pattern of acute bacillary dysentery. In chronic *Salmonella* infections it was possible to obtain high titer fecal agglutinins on one or more occasions during the period of observation. In chronic ulcerative colitis it was found that relatively high-titer fecal agglutinins for at least one species of *Shigella* were present during episodes of exacerbation of symptoms.

It is of some interest that, in those instances in which positive cultures were obtained, fecal agglutinins were found in highest titer during the period in which presumably the greatest numbers of the causative organism were excreted, *i.e.* during greatest activity of the infection, but disappeared after recovery was established. Although it is not clear as to the origin of fecal antibodies in these infections, it is significant from a diagnostic point of view, and presumably for initiation of recovery, that antibody is excreted during the active phase of the infection or, in the case of chronic infections, during periods of clinical activity of the disease. The diagnostic utility of these observations is obvious, for in instances in which no etiologic agent can be found, the presence of fecal agglutinins appears to indicate, indirectly at least, the probable causative organism. The finding of fecal agglutinins for various species of *Shigella* from patients suffering from chronic ulcerative colitis is interesting with respect to Felsen's (*3*) views on the relation of bacillary dysentery to chronic ulcerative colitis. More important from the point of view of the patient is the role coproantibody plays in initiating recovery; that it is not completely effective in some instances is indicated by finding fecal agglutinins to high titer in chronic forms of enteric infection. Under such conditions however, the demonstration of coproantibody parallels evidence of clinical activity of the disease, even though the infectious agent is not recovered.

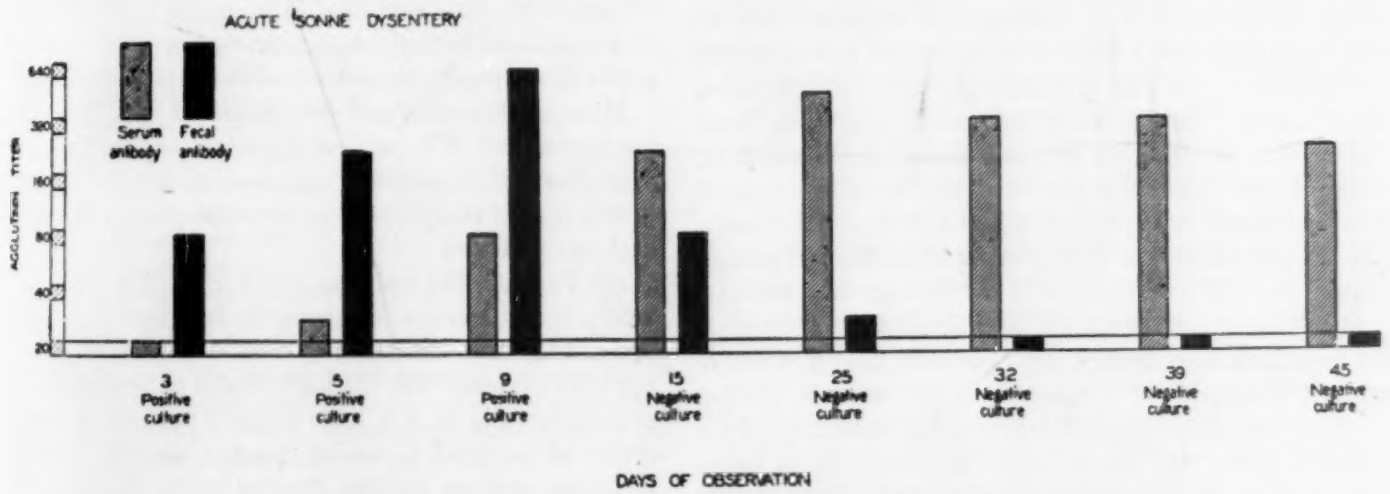

FIG. 1. Summary of serum and fecal agglutinin response in acute bacillary dysentery.

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Atherosclerosis and Alimentary Hyperlipemia[1]

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The purpose of this communication is to report investigations which demonstrate that the physical state of the plasma lipids is the same during alimentary hyperlipemia as in those sustained hyperlipemic conditions that are known to predispose to the relatively rapid and severe development of atherosclerosis. The many extensive studies on plasma cholesterol concentrations have failed to provide the answer to the usual development of some degree or another of this slow process of intimal lipid deposition in most otherwise normal persons (*6*, *7*, *9*). It is here proposed that it is because only lipid *concentrations* have been investigated, and primarily in the postabsorptive (fasting) state, that the clue to the underlying etiology of atherosclerosis has been missed.

The investigation of the physical state of the plasma lipids in normal humans and animals, and under various pathological, physiological, and experimental conditions, and the correlation of these data with the pathogenic development of atherosclerosis, have been the focal points in our studies (*6*). Our approach to the study of the actual physical state and particle size of the plasma lipids has involved three simple methods:

(1) *Direct observation and photomicrography of high-power, dark-field preparations:* This method does not lend itself to accurate quantitative estimations, but does providedirect visual observation of only the larger colloidal lipid particles, which appear as bright points of light of varying sizes. These particles are in Brownian motion to a greater or lesser degree, according to their size. This technique has in the past been of occasional interest to physiologists in the study of fat absorption. Gage and Fish (*5*) in 1924 demonstrated that the plasma of normal humans and animals in the fasting state contains very few lipid particles which are of sufficient size to be visible in the dark field. After a fatty meal, however, large and visible particles ("chylomicrons") appear in great numbers. During this alimentary hyperlipemia the chemical concentration of the fat in the plasma may be increased by one-fourth to three-fourths, but the number of chylomicrons seen in the dark field may be increased 10- to 20-fold. This has two rather obvious implications: (a) In fasting plasma specimens the lipids are for the most part carried in very small and invisible colloidal particles; (b) the striking disproportion between the marked increase in visible lipid particles as compared with the relatively slight increase in chemical concentrations is evidence that the average particle size of these absorbed lipids is much greater than is found in the fasting state or after a nonfatty meal.

Our observations were first directed, however, toward the study of the dark-field picture in sustained hyperlipemia, *i.e.* in humans with hyperlipemic diabetes mellitus, myxedema, nephrosis, and xanthomatosis, in cholesterol-fed rabbits and chickens, and in stilbestrol-injected chickens. In these hyperlipemic states the dark field reveals, in a single oil-immersion field, hundreds to thousands of lipid particles which are of sufficient size to be directly visible by light reflection. These are of varying sizes, and many are so large as to exhibit little or no Brownian motion. This is a markedly different picture than that found in the plasma of normal fasting subjects or after a fat-free meal where only a very few (20–30) tiny, dancing lipid particles can be found in each field; furthermore, these few visible particles in fasting plasma appear for the most part as dull specks and are at the extreme lower limit of detection in the dark field. From our later studies on alimentary hyperlipemia it became obvious that the *hyper-* and *macrochylomicronemia* that follow the ingestion of a lipid-rich meal reproduces the same condition of increased particle size and coarser particulate distribution of the lipids in the plasma as found in sustained hyperlipemia of pathological or experimental origin. (These new terms are used as descriptive of the condition of markedly increased numbers of large lipid particles in the plasma.) Although a fatty meal causes only a slight and insignificant elevation in plasma cholesterol concentrations, it nevertheless does reproduce for 3–5 hours this same pronounced alteration in the physical state of the plasma lipids (increased particle size) that is found to be characteristic of those sustained hyperlipemic states that result in the early and severe development of lipid deposition in the arterial intima.

Microscopic counts and estimations of particle size in fasting plasma and in hyperlipemic plasma are quite impractical. Therefore, other methods were needed for the quantitative comparison of the physical state of the plasma lipids in these various conditions.

(2) *Tyndall effect and nephelometry:* Lipid particles in dark-field preparations are demonstrated only by a light-scattering effect. This light-scattering by a medium containing colloidal particles increases with the particle size as well as the number of particles present. A reliable means of comparing the physical status of the lipids in various plasma samples resides in the quantitative study of their Tyndall effect. Plasma (or serum) specimens that scatter the most light are those containing the greater number of larger lipid particles. The relatively small amount of light-scattering due to the plasma proteins may be considered part of the normal baseline. It is evident, then, that measuring the intensity of the light scattered at right angles by a standard amount of plasma and a standard light beam will give a fair quantitative estimation, for comparative purposes, of the physical state of the plasma lipids. Therefore, an especially designed photoelectric nephelometer was constructed for this purpose. Typical comparative values found by this method are given in Table 1.

(3) *High-speed centrifugation:* Stoke's law states that the rate of settling of particles from a liquid medium is dependent on the size of the particles and that larger particles settle (to the top or bottom, depending on specific gravity) more rapidly than smaller ones. When plasma is centrifuged, the larger particles of the plasma lipids will rise to the top more readily than

[1] This is an introductory article to a series of reports on atherosclerosis which are to follow from this laboratory. Gratitude is expressed for the invaluable encouragement and criticism of this work by the late Joseph Edgar Tyree; the author also wishes to acknowledge the aid of L. G. Moench, of the University of Utah Medical School and the Salt Lake Clinic, and also F. L. Stauffer. The photoelectric nephelometer was constructed with the technical assistance of F. S. Stauffer, C. L. Peterson, and R. H. Starley. This instrument, along with the design and theory of nephelometry as applied to the study of the physical state of the plasma lipids, will be reported in detail in a subsequent communication.

[2] The early part of this work was done while the author was at the Harvard Medical School and on the resident staff of the Massachusetts General Hospital.

the smaller ones. When samples of serum or plasma are spun at moderately high speeds (*i.e.* 16,000–18,000 r.p.m.) in the same rotor for a given length of time, those containing greater numbers of larger particles will give a wider 'cream line' or thicker layer of lipid particles which have risen to the top than is found in those plasma samples with a smaller average lipid particle size. Estimation of the volume per cent occupied by the lipid particles which have come to the top provides, therefore, another method for the study and comparison of the physical state of the plasma lipids.

TABLE 1

Subject	Tyndall light (microamperes)
In the postabsorptive state:	
Average of 20 normal humans, fasting	34
" "8 rabbits on normal diet, fasting	28
" "8 steers " " " "	26
Sustained hyperlipemia:	
Average of 6 rabbits after 10 weeks cholesterol feeding	980
" "5 stilbestrol-injected chickens	740
Diabetic patient with sustained hyperlipemia	720
" " " " "	540
" in acidosis	820
Nephrotic with sustained hyperlipemia	620
Essential xanthomatosis with sustained hyperlipemia	890
Alimentary hyperlipemia:	
R.L.T., normal adult human, fasting	28
4 hours after 50 grams of butter fat	140
S.M., normal adult human, fasting	40
4 hours after 50 grams of butter fat	156
R.A.P., normal adult human, fasting	31
4 hours after 50 grams of butter fat	159
B.B.P., normal adult human, fasting	24
4 hours after 50 grams of butter fat	93
C.L.P., normal adult human, fasting*	91
4 hours after 50 grams of butter fat	433
R.H., normal adult human, fasting	29
4 hours after 50 grams of butter fat	184
A.B.L., normal adult human, fasting	32
4 hours after 50 grams of butter fat	137
M.A.E., normal adult human, fasting	44
4 hours after 50 grams of butter fat	280

* Repeated tests on this otherwise normal man have shown him to be unusually sensitive to the development of *hyper-* and *macrochylomicronemia* following various fat-rich test meals. We have noted others who have similarly been exceptionally sensitive in this regard to fatty meals.

There is a fairly reliable degree of correlation between comparative estimates of the physical state of the plasma lipids by the above three methods. That the lipid particles in the plasma following a fatty meal contain cholesterol has been readily demonstrated by analysis for cholesterol of the lipid layer that comes to the surface as a result of high-speed centrifugation (*6*). This is true even after a cholesterol-free fatty meal, *i.e.* olive oil; the logical source of this cholesterol is the bile which is called forth in large quantities for the emulsification of a fatty meal. It is not surprising that chylomicrons contain cholesterol as well as triglycerides and fatty acids; for, being lipids which are both insoluble in water and mutually soluble in each other, they may be expected to be found together in the same lipid particles, rather than carried each in separate micelles.

In summary, it has been found that during the 3–5 hours following a fatty meal the physical state of the lipid particles appearing in the plasma is qualitatively the same as in sustained hyperlipemia. This alteration in physical state consists of markedly greater numbers of lipid particles of considerably larger size than those found in normal fasting plasma or after fat-free meals. From these studies the theory is here put forth that the cumulative effect of many fatty meals over a lifetime, by producing these transient showers of large lipid particles in the plasma, may be the underlying cause of the intimal lipid deposition in human atherosclerosis. This deposition takes place primarily in the tissue spaces of the arterial intima between the overlying endothelium and the underlying barrier of the fenestrated internal elastic membrane (*1*). The lipid particles must be assumed to be retained and deposited from the plasma-derived nutrient lymph stream which normally passes from the lumen through the intramural structures toward the adventitial venules and lymphatics (*1*). It may be theorized that the increased particle size of the lipids in sustained or alimentary hyperlipemia is the stimulus to the phagocytosis in the intima by macrophages and the formation of the typical 'foam cells.' The barrier function of the fenestrated or even reduplicated internal elastic membrane may have an important role in the mechanics of the process of lipid-particle retention in the intimal tissue spaces (*1, 6*). The neutral fats and fatty acids in the depositing lipid particles are more readily resorbed and removed (by the action of macrophages and tissue-fluid enzymes) than cholesterol and cholesterol esters, which remain as the difficult-to-remove residue (*6*). Christianson (*3*) has shown this experimentally by demonstrating that if a mixture containing 95 per cent fat and 5 per cent cholesterol is injected intramurally and deposited in the arterial wall with a fine hypodermic needle, the resultant lipid lesion soon consists primarily of cholesterol due to the much more rapid resorption and removal of the fats and fatty acids from the deposit.

Circumstantial evidence on the occurrence of atherosclerosis supports this chylomicron theory of etiology as above outlined: (a) Atherosclerosis is rare in peoples who eat very low or nearly fat-free diets, *i.e.* Chinese and Okinawans (*8*); (b) atherosclerotic disease decreased notably in Germany during the fat-shortage years immediately following World War I (*2*); (c) atherosclerosis is more common in obese, overnourished persons than in the lean and undernourished; (d) it is often less severe and less common in chronic alcoholics (who eat less, especially less fat, for which they often have intolerance) than in nonalcoholics (*6*); (e) intimal lipid deposition and atherosclerosis are rare and minimal in wild animals (including the herbivorous anthropoid apes), which seldom, if ever, eat a meal containing the amount of fat found in the average human diet (*1, 4*).

This theory, along with a thorough review of the literature and further investigations from this laboratory, will be presented in full in a forthcoming monograph (*6*).

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IN THE LABORATORY

Penicillin Types Produced by *P. Chrysogenum* Q-176

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The organism *P. chrysogenum* Q-176 (*1*) has been widely used for the commercial production of penicillin. It has been recognized that this mold can produce several types of penicillin, although the literature (*4*) is not clear on the number of different penicillins actually produced.

It has now been found that Q 176, grown on the usual corn steep liquor-lactose medium apparently can produce at least 8 penicillins. These include the common types (*2*), namely, G-penicillin (benzylpenicillin), F-penicillin (Δ^2-pentenylpenicillin), what is probably dihydro-F-penicillin (n-amylpenicillin), K-penicillin (n-heptylpenicillin), and X-penicillin (p-hydroxybenzylpenicillin). In addition, three other penicillin types have been demonstrated to be produced in small amounts by this organism.

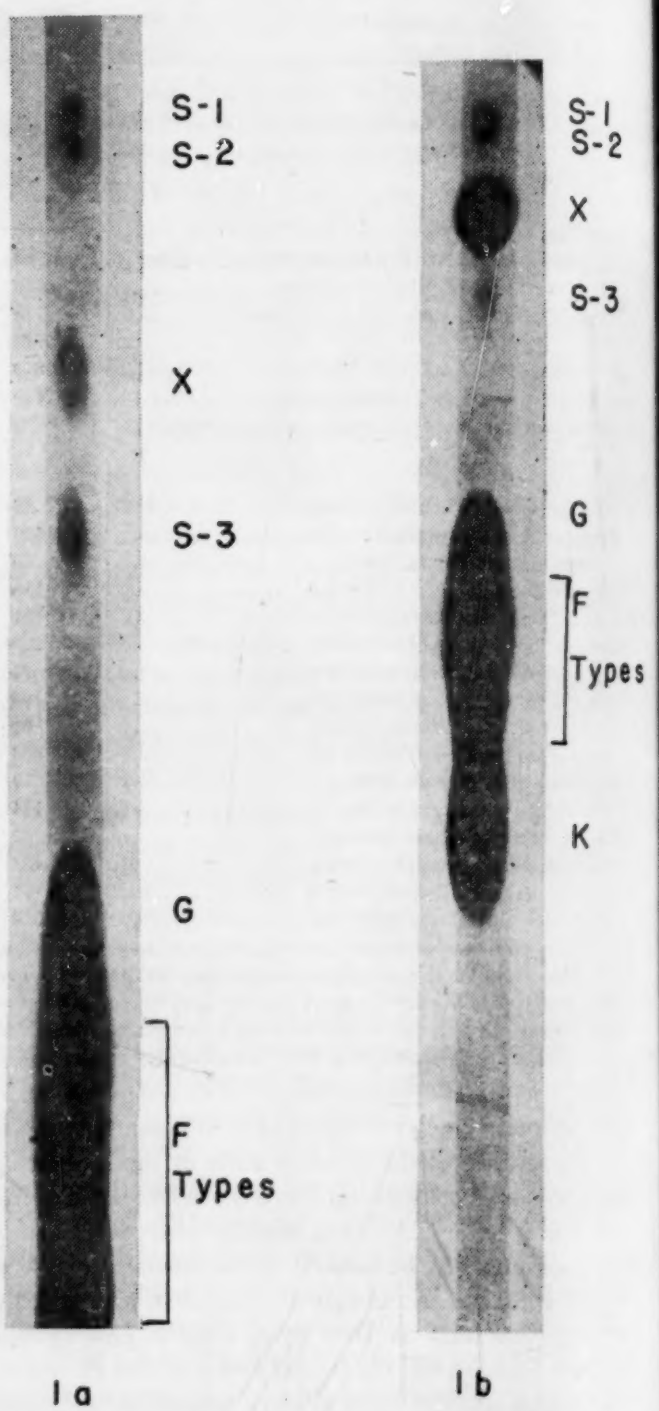
In proving the presence of the indicated penicillins, a paper partition chromatographic method similar to that described by Goodall and Levi (*3*) has been used. These workers obtained evidence for the existence of penicillins other than F (I), G (II), X (III), and K (IV), but did not state the origin of such penicillins.

In determining the types of penicillin present in Q-176 fermentation broth, the method of Goodall and Levi was modified. Thus, the chromatograms were developed at room temperature (about 24°C.), in a 2- to 4 hour period, using Whatman #4 paper strips buffered at pH 5 0 with 25 per cent phosphate buffer, and amyl acetate as the developing solvent. The fermentation broth was adjusted to pH 5.0 before taking an 0 008-ml. drop for analysis.

After developing the chromatograms, the strips were air dried and placed on FDA agar plates which had previously been seeded with *Staph. aureus* 209P. The plates were incubated at 37° C. for 18 hours.

In looking for penicillins which may be present in trace quantities in a fermentation broth, it was found necessary to remove the paper strips from the agar plates after termination of the period of bacterial growth. Upon removing the strips, one frequently notes the presence of zones of inhibition which were too small to extend beyond the covering paper strip; there is sufficient bacterial growth beneath the strip to delineate such zones clearly.

In Figs. 1a, 1b, and 2 are shown the results obtained using the paper chromatographic method of analysis as applied to 5-day-old *P. chrysogenum* Q-176 fermentation broth, the photographs being taken after removal of the paper strips from the agar plates. The organism Q-176 was grown in the usual corn steep liquor-lactose medium (4.5 per cent corn steep liquor by volume, 2 per cent lactose by weight) without addition of specific penicillin precursors.



FIGS. 1a and 1b: Chromatographic analysis of undiluted 5-day-old *P. chrysogenum* Q-176 fermentation broth.

In Fig. 1a two small, separate zones of inhibition, designated S-1 and S-2, can be noted. These zones are due to penicillin types not hitherto reported as being produced by Q-176. Proof that they are due to penicillin-type antibiotics will appear below.

[1] The authors wish to thank E. C. Williams, director of research, for his encouragement and suggestions in this work. Thanks are also extended to Harry Eagle for the gift of pure penicillins X, F, and K.

The third zone from the top has been shown to be due to penicillin X. This was accomplished by adding known penicillin X to a fermentation broth and then chromatographing. Only the third zone was enlarged by the added penicillin X (Fig. 1b). In this case the chromatogram was not developed sufficiently to show the complete separation of penicillins S-1 and S-2.

The fourth zone from the top, designated as S 3, represents a third new penicillin type.

The penicillin types S-1, S-2, X, and S-3 are followed on the chromatogram by a multiple connected zone of inhibition, part of which may be seen in Fig. 1a. It has been found that this multiple zone consists of at least four parts, due to four penicillins: G, F, possibly dihydro-F, and K.

In order to show the component parts of the connected zone, it is advisable to use a diluted fermentation broth; otherwise, there may be a marked overlapping of zones which makes it difficult to see the true nature of their multiplicity

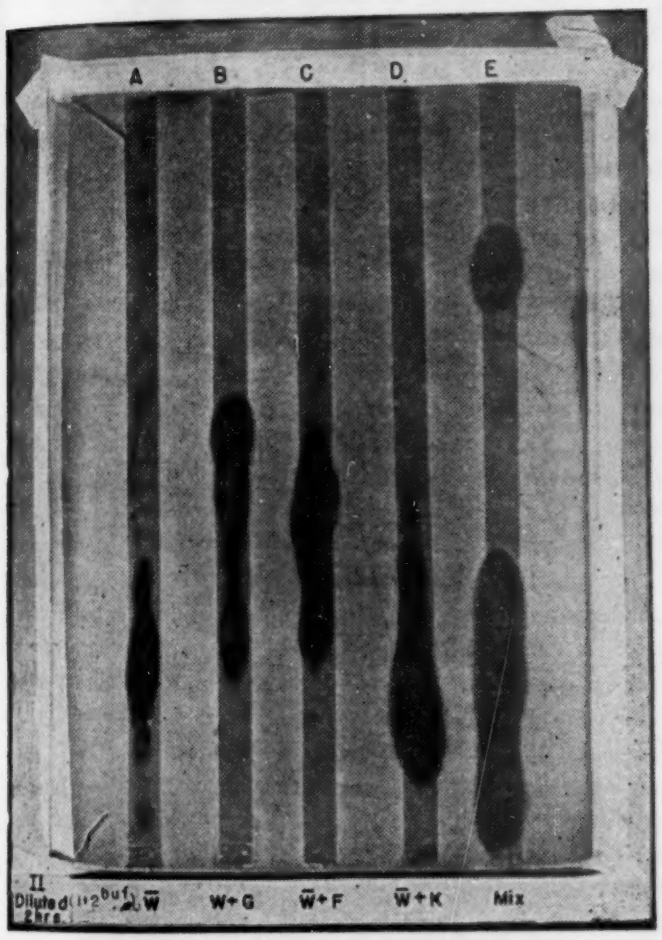


FIG. 2: Chromatographic analysis of 5-day-old *P. chrysogenum* Q-176 fermentation broth diluted to contain 75 units/ml.

Fig. 2 shows the results of an experiment designed to identify the component penicillins responsible for the connected zone of inhibition. In obtaining the results indicated in strip A, a sample of fermentation broth of Q-176 diluted to 75 units/ml. was chromatographed. Four zones, indicated by either separate ellipses or bulbous swelling formed by overlapping ellipses, show the presence of at least four different penicillin types.

These four zones were identified, by adding in turn to the same broth samples of pure, known penicillins, then chromatographing and observing which of the four zones was accentuated by the addition. The modified chromatograms so obtained revealed the identity of the penicillin types observed in the original chromatogram.

In this way, the first zone in chromatogram A of Fig. 2 was identified as being due to penicillin G (see modified strip B); the second zone was identified as being due to penicillin F (see modified strip C); the third zone was tentatively ascribed to dihydro-F, but without confirmation, because no unequivocal sample of dihydro-F was available for comparison; and the fourth zone was identified as being due to penicillin K (see modified strip D). It is to be noted that, due to some artifact, the K zone in strip A is smaller relative to the other zones than is usually the case. Thus, the K zone in strip B is more typical of the size and shape of the K zone relative to the other zones.

Strip E in Fig. 2, representing the results of chromatographic analysis of a mix of known penicillins X, G, F, and K, demonstrates the well-defined separation of the X zone and the overlapping tendency of the G, F, and K zones.

That all the zones observed in the paper chromatographic analysis of Q-176 broth are due to penicillin-type antibiotics is evidenced by the fact that these antibiotics are all destroyed by penicillinase.

It would appear, therefore, that *P. chrysogenum* Q-176 can produce no less than 8 penicillins when grown on the usual corn steep liquor-lactose medium. Four of these, S-1, S-2, X, and S-3, are produced in small quantities; in addition, four other well-known types, G, F, what is probably dihydro-F, and K, are also formed. The new penicillins S-1, S-2, and S-3 have not as yet been characterized chemically.

Addendum: Since submitting this paper, our attention has been called to a report (National Institute of Health release) presented by C. J. Salivar, V. V. Bogert, and E. V. Brown at the Conference on Antibiotic Research held in Washington, D. C., January 31 and February 1, 1947, under the auspices of the Antibiotics Study Section of the National Institute of Health. These workers have reported that Q-176 may produce Δ^2-pentenylpenicillin as well as possibly one or two additional penicillins which may be related to penicillin K. The method of analysis used by Salivar, *et al.* was a column chromatographic method supplemented by the Craig countercurrent distribution method, using ether as the solvent. We have found that the order in which the different penicillins appear in our paper chromatograms does not change whether ether or amyl acetate is used. Since the new penicillins we are reporting, namely, S-1, S-2, and S-3, have solubility characteristics more closely allied to penicillin X, they are probably not identical with those reported by Salivar, *et al.*, which are similar in solubility characteristics to F and K. Using the paper chromatographic method of analysis, only two F types and one K type of penicillin were observed. This may be due to the inability of the paper chromatogram to differentiate Δ^2-pentenylpenicillin and the new K-types suggested by Salivar, *et al.* It would seem, therefore, that according to our work and that of Salivar, *et al.*, Q-176 can produce as many as 11 penicillins.

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Use of Trisodium Phosphate in Microscopical Technic

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The writers (*2*) published a preliminary report on the use of trisodium phosphate as a reagent for reclaiming preserved zoological specimens which have become dry by the complete evaporation of the preserving liquid. Discovery of this method was incidental to a series of studies in which various detergents were used to facilitate penetration of fluids in the preparation of microscopic mounts of parasitic worms. A series of memoranda by Hance (*1*) called attention to the fact that wetting agents added to fixing reagents hasten the penetration of the killing fluids into the tissues. Dr. Hance also pointed out that a wetting agent increases the speed with which many staining reactions are accomplished, while, added to albumin fixative, it makes the spreading of paraffin ribbons much more certain. In addition to these uses in microscopic technic, the present writers have found that the action of trisodium phosphate on preserved parasitic worms seems to increase noticeably the permeability of tissues to all the histological reagents. The effect upon the tissues seems to be much more profound than would be accounted for by the chemical merely reducing the surface tension of the fluids. Entire histologically fixed organisms become much softened when treated with trisodium phosphate, but there is no apparent damage to the tissues such as occurs when potassium hydroxide is used.

For many years in this laboratory serious difficulties have been encountered in securing permanent whole mounts of Acanthocephala. Similar difficulties are often experienced in handling nematodes and other organisms intended for microscopic study. Very commonly, stained specimens, after careful dehydration and clearing, turn chalky white and become entirely opaque after being introduced into balsam or clarite. To avoid this, it became routine procedure to prick the body wall of all specimens with a very fine needle before placing them in stain. By using a dissecting binocular, the perforations may be made in places where relatively little damage to the body wall or underlying structures results. However, in many instances internal organs are injured, and in all cases the punctures mar the appearance of the finished mounts.

It should be recalled that the entire body of all acanthocephalans is completely invested by a thin, noncellular cuticula. This plays an important role in the life processes of the worm and, even following death, continues to determine the passage of fluids through the body wall in both directions. Since there is not the slightest vestige of digestive organs at any developmental stage, the living worm must absorb all of its nutrients through its body surface. During life a very delicate balance is maintained between the fluids within the worm and those in the surrounding medium. As long as normal conditions are maintained, the body is flat and flaccid; when the living worm is removed to normal salt solution or water for microscopic examination, this balance becomes disturbed. Fluids pass through the wall, causing the body to become turgidly distended and circular in cross section. Many zoologists have failed to realize that this turgid state is due to a physiological response to abnormal surroundings and hence have classified Acanthocephala as "round" worms. Since the plumped condition is almost universally distinctive of all well-preserved specimens, it should be maintained through dehydration and clearing after the specimens have been stained and prepared for microscopic mounts.

Alcoholic specimens are passed down the grades of alcohol to water and are then placed in a solution of approximately .25 per cent of trisodium phosphate in distilled water. Freshly preserved specimens become soft, pliable, and translucent almost immediately, while specimens that have become hard, brittle, and unyielding after long preservation may require several hours or even days in a warming oven before they attain the proper degree of softness and pliability. It is well to keep treated material under observation, since the use of too strong solutions of trisodium phosphate or weaker solutions over too long a time may render specimens too soft and jelly-like for easy handling. When the desired degree of softness and translucency has been reached, they should be removed to distilled water to check the action.

Specimens thus treated, washed in distilled water, and subjected to hematoxylin or borax carmine stain become much more brilliantly stained than untreated specimens. Furthermore, the treated specimens may be dehydrated, cleared, and mounted in clarite or damar without developing opacity except in rare instances. This treatment is far superior to the puncturing mentioned previously.

Specimens of Acanthocephala which have been completely dried for many years have been reclaimed by the foregoing process. In some instances, practically all details of internal structure became available in the stained mounts; in others, only structures like proboscis hooks and body spines. With preserved specimens which are shriveled and hardened the strength of the solution is increased. Worms which are fairly turgid in preserving fluid usually become soft and flaccid in trisodium phosphate. Later, when returned to water or alcohol grades, the turgidity reappears. One distinct advantage of the softening effect is the ease with which specimens may be straightened prior to dehydration. While softened, each specimen may be folded back and forth on a microscopic slide along strips of cardboard or toothpicks and may be slightly compressed and held in place by covering with another slide. Several wrappings of thread provide the pressure and hold the slides together so that the stained specimen may be carried in Coplin or Harvard jars through the grades of alcohol. In absolute alcohol the specimen becomes firm enough that it may be removed from between the slides and yet retain its series of folds, ready for clearing and mounting under a cover glass. Such a preparation may be "read" under the microscope in much the same way that series of sections are interpreted, without the confusion of parts usually encountered when long worms are broken into lengths suitable for mounting. Large worms intended for partial dissection to show internal organs are much more readily handled after treatment with trisodium phosphate.

No other detergent tried in this laboratory has given results superior to those obtained with commercial grade of trisodium phosphate, which has the distinct advantage of low cost and general availability.

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